

REMARKS/ARGUMENTS

The Objection to the Specification Should be Withdrawn

The specification has been objected to for the informality of misspelling “PCR” on page 34 as “PCT”.

Applicants have amended the specification to correct this inadvertent typographical error. This amendment to the specification is purely formal in nature and does not introduce new matter. Accordingly, Applicants submit that this objection should be withdrawn.

Status of the Claims

Applicants respectfully acknowledge that the Examiner has allowed claims 20 and 24 and that the Examiner has also indicated that claims 21 and 22 would be allowable if re-written in independent form including all of the limitations of the base claim and any intervening claims and following the correction of the base claim, claim 15, to overcome the objection to that claim.

Claims 1, 6, 9, 15, 21, 22, and 30 have been amended.

Claims 1, 6, and 9 have been amended to point out more distinctly that the claimed methods for detecting a mutant allele of a wheat *AHASL* gene each involve detecting a product of said PCR amplification that corresponds to the region of said *AHASL* gene bounded by the annealing sites of the mutant-allele-specific primer and the reverse *AHASL*-gene-specific primer on said *AHASL* gene. Support for this amendment can be found in original claims 1, 6, and 9 and in the specification, particularly in the first paragraph on page 19.

Claims 1, 15, and 30 have been amended to add the word --rise-- immediately after “gives” in the recitation “gives to the S653(At)N in response to a claim objection discussed below. This amendment is purely formal in nature and is fully supported by the original claims and specification.

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Claims 21 and 22 have been amended to independent form by incorporating the limitations of claim 15 including the amendment described above to address the objection to claim 15. The amendment of claims 21 and 22 is purely formal in nature and does not introduce new matter.

No new matter has been added by way of amendment of the claims.

Claims 1-9, 14-24, and 29-31 are pending.

Reexamination and reconsideration of the application as amended are respectfully requested in view of the following remarks.

The Objections to the Claims Should be Withdrawn

Claims 1, 15, and 30 have been objected to for the informality of an omitted word. In particular, the word "rise" was omitted immediately after the word "gives" in each of these claims. Applicants have amended these claims to add the missing word --rise-- as suggested by the Examiner.

Claims 21 and 22 have been objected to for being dependent upon a rejected base claim. The Office Action further indicates that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim, claim 15, and the suggested correction of this claim to overcome the objection to it. Applicants have amended claims 21 and 22 to independent form by including all of the limitation of base claim 15 and the addition of the word --rise-- as described in the paragraph immediately above.

In view of the amendments to claims 1, 15, 21, 22, and 30, the objections to these claims should be withdrawn. Furthermore, Applicants submit that claims 21 and 22 are now in allowable form.

The Rejection of the Claims under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-9 and 14 have been rejected under 35 U.S.C. §112, second paragraph, for

indefiniteness. Claims 1, 6, and 9 have been amended. This rejection is respectfully traversed.

The Office Action indicates that claims 1-9 and 14 are unclear because while the preamble states “method for detecting a mutant allele”, there is not a step in which any mutant allele is detected. The Office Action suggests amending step (c) of each of these claims to define a step of allele detection as provided in the specification.

Applicants respectfully disagree with the position of the Office Action that claims 1-9 and 14 are indefinite for not reciting a step in which a mutant allele is detected. One of ordinary skill in the art in view of the instant specification would readily understand that the recitation of “detecting the products of said PCR amplification” in step (c) of each of these claims includes the detection of a PCR product corresponding to the mutant allele. In the interest of furthering prosecution and not to limit the scope of their invention, Applicants have amended each of these claims to point out more distinctly that the detecting step involves “detecting a product of said PCR amplification, said product corresponding to the region of said *AHASL* gene bounded by the annealing sites of the mutant-allele-specific primer and the reverse *AHASL*-gene-specific primer on said *AHASL* gene”.

In view of the amendments and the above remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-5, 8, 14-19, 23, and 29-31 have been rejected under 35 U.S.C. § 103(a). Claims 1, 15, and 30 have been amended. This rejection is respectfully traversed.

Claims 1, 8, 14, 15, 23 and 29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hucl *et al.* (WO 2003/014357) in view of Liu *et al.* (1997, *Genome Res.* 7:389-398) and Kwok *et al.* (1990, *Nucl. Acids Res.* 18:999-1005). Regarding claim 1, the Office Action indicates that Hucl *et al.* teaches resistance to imidazolinone can be conferred by an guanine to adenine substitution in the AHASL1 gene which results in an asparagine to serine substitution, the nucleic acid and deduced amino acid sequences of AHASL1 genes from several

wheat imidazolinone resistant wheat plants, the detection of such genes by amplifying AHASL1 genes, the use of genomic DNA, and the portions of the AHASL1 nucleic acid sequences responsible for the imidazolinone mutation. Regarding claim 8, the Office Action indicates that Hucl *et al.* teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant and additionally teaches the sequence of the Imi1 gene wheat gene, which is the AHASL1D gene on the D genome as evidenced by Pozniak *et al.* (2004). Regarding claims 15 and 23, the Office Action indicates that the teachings of Hucl *et al.* are applied to steps (a), (b), and (d) of claim 15 as they were applied to claims 1 and 8 and that Hucl *et al.* additionally teaches the wild-type AHASL1 nucleic acid sequence that includes the sequence relevant to SEQ ID NO: 10 of the instant application. Regarding claim 23, the Office Action indicates that Hucl *et al.* teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant, and the sequence of the Imi1 gene wheat gene, which is the AHASL1D gene on the D genome as evidenced by Pozniak *et al.* (2004).

The Office Action acknowledges that Hucl *et al.* fails to teach the analysis of AHASL1 genes via allele-specific PCR using oligonucleotide primers, or primers with mismatches as are required for primers directed to nucleotides 3 to 23 of SEQ ID NO: 12 with a cytidine at the 3' end.

The Office Action indicates that Liu *et al.* teaches a method for the detection of single nucleotide polymorphisms using allele-specific primers. The Office Action indicates that Liu *et al.* teach a PCR reaction comprising genomic DNA, dNTPs, a polymerase, forward and reverse gene-specific primers, and a mutant-allele-specific primer, examples in which the mutant and wild-type allele-specific primers are designed to flank the polymorphic position and the detection of PCR products using gel electrophoresis and ethidium bromide staining, an allele-specific primer that is capable of annealing to a region of the analyzed gene that is nested between the annealing sites of the gene-specific primers, and the use of wild-type allele-specific primers for detection of wild-type alleles.

The Office Action acknowledges that neither Hucl *et al.* nor Liu *et al.* teach the use of an allele specific primer with a 3'-terminal cytidine where said primer is used to detect an A

nucleotide allele by specifically hybridizing with T in the template nucleotide.

The Office Action indicates that Kwok *et al.* provides general teachings concerning the use of different 3' terminal nucleotides in the amplification of template bases, the refractory nature of a 3' terminal C in the amplification of a C-containing template, and the ability of a primer containing a 3' terminal C in the amplification of a T-containing template.

The Office Action asserts that it would have been *prima facie* obvious to one of skill in the art at the time of the invention was made to have modified the mutation detection methods of Hucl *et al.* so as to have used the allele-specific and gene specific primers of Liu *et al.* and a primer with a 3' terminal C for the specific amplification of the mutant allele. The Office Action further asserts that one would have been motivated to use the methods of Liu *et al.* based on the teaching of Liu *et al.* that a nested allele-specific amplification method provides an internal positive control to us a mutant allele-specific primer with a 3' terminal C for the detection of the mutation allele based on the teaching of Kwok *et al.* that such a primer will amplify a T nucleotide template but not a C nucleotide template.

In contrast to this position of the Office Action, Applicants' claimed invention is not obvious in view of the combination of Hucl *et al.*, Liu *et al.*, and Kwok *et al.* Applicants' claimed invention is directed to oligonucleotide primers and methods for detecting a mutant allele of a specific, wheat *AHASL* gene and for analysis of a wheat *AHASL* gene. The methods of Applicants' claimed invention involve the use of a mutant-allele-specific primer that has a cytidine as the 3'-end nucleotide and that is capable of annealing to the complement of nucleotides 3 to 23 of SEQ ID NO: 12. As disclosed in the instant specification on pages 7, 17, 18, such a mutant-allele-specific primer, when annealed to mutant AHASL allele template, results in a mismatch at the 3'-end nucleotide of the primer and the site of the G-to-A point mutation in the mutant AHASL allele template, yet allows for the unexpected PCR amplification of the mutant AHASL allele but not the wild-type AHASL allele. As explained in the specification on pages 17-18, Applicants invention was both surprising and unexpected in view of the teachings of Newton *et al.* (1989) *Nucl. Acids Res.* 17:2503-2516 and Wu *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86: 2757-2760 that oligonucleotides with a 3'-end-residue that is

mismatched to the template DNA will not function as a primer for PCR amplification under appropriate conditions.

Furthermore, the DelRio-LaFreniere *et al.* reference (2001, *Mol. Diagn.* 6:201-209), which was cited in the claim rejections under 35 U.S.C. § 103(a) in the final Office Action of December 22, 2006, also teaches away from Applicants' claimed invention. As discussed in detail in Applicants' last response to the Office, the DelRio-LaFreniere *et al.* reference teaches away from primers with mismatches at the 3'-end nucleotide, in favor of mismatches at the penultimate and antepenultimate bases at the 3' end of the primer. Thus, one of ordinary skill in the art would not find that the teachings of Kwok *et al.* render obvious Applicants' claimed invention when combined with Hucl *et al.* and Liu *et al.* because such a person would also be familiar with the conflicting teachings of the DelRio-LaFreniere *et al.*, Newton *et al.* and Wu *et al.* reference.

The Examiner is respectfully reminded that he is not permitted to select in hindsight only those references that allegedly support a prima facie case of obviousness while ignoring those teachings that are in direct conflict to one or more of the teachings upon which the prima facie case of obviousness depends. According to MPEP § 2143.01 II, "[w]here the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another." The record fails to provide any evidence that Examiner has properly considered the degree to which the Kwok *et al.* reference might accurately discredit the DelRio-LaFreniere *et al.*, Newton *et al.*, and Wu *et al.* references. Therefore, Applicants respectfully invite the Examiner either: (i) to state with particularity in the next Office Action why one of ordinary skill in the art at the time of the invention would have considered that the Kwok *et al.* reference accurately discredits the teachings of the DelRio-LaFreniere *et al.*, Newton *et al.*, and Wu *et al.* references when considered alone or in combination; or (ii) to withdraw this rejection.

The Office Action provides two additional rejections under 35 U.S.C. § 103(a) that depend on the combination of the Hucl *et al.*, Liu *et al.*, and Kwok *et al.*, and either one or two

additional references. Claims 2, 4, 5, 16, 18, 19, and 30 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hucl *et al.* in view of Liu *et al.* and Kwok *et al.* and in further view of Stanton (2002, US Patent No. 6,475,736). Claims 3, 17, and 31 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hucl *et al.* in view of Liu *et al.* and Kwok *et al.* and Stanton and in further view of Werle *et al.* (1994, *Nucl. Acids Res.* 20:4354-4355).

Because each of these two obviousness rejections depend on the Kwok *et al.* reference, Applicants respectfully submit that the Examiner has not made prima facie cases for obviousness due to the failure to address the conflicting references as discussed in detail above. Therefore, Applicants again respectfully invite the Examiner either: (i) to state with particularity in the next Office Action why one of ordinary skill in the art at the time of the invention would have considered that the Kwok *et al.* reference accurately discredits the teachings of the DelRio-LaFreniere *et al.*, Newton *et al.*, and Wu *et al.* references when considered alone or in combination; or (ii) to withdraw these rejections.

In view of the amendments and the above remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the objections to the claims and the rejections under 35 U.S.C. §§ 103 and 112, second paragraph, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. In any event, the Examiner is respectfully requested to enter the above amendments for the purpose of furthering prosecution.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of

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this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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